Award Number: W81XWH-05-1-0401

TITLE: Identification of Biomarkers Associated with the Healing of Chronic Wounds

PRINCIPAL INVESTIGATOR: Laura E. Edsberg, Ph.D.

CONTRACTING ORGANIZATION: Daemen College
Amherst, NY 14226

REPORT DATE: January 2008

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	**2. REPORT TYPE**	**3. DATES COVERED** *(From - To)*
01-01-2008	Final	15 JUN 2005 - 31 DEC 2007

4. TITLE AND SUBTITLE
Identification of Biomarkers Associated with the Healing of Chronic Wounds

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-05-1-0401

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Laura E. Edsberg, Ph.D.

E-Mail: ledsberg@daemen.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Daemen College
Amherst, NY 14226

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
It is the objective of this study to identify the biomarkers associated with the earliest stages of healing in chronic wounds. The findings of this study are intended to facilitate the development a diagnostic tool, which could be used to evaluate the healing process. Samples have been collected from interior and peripheral wound sites over 6 weeks from 48 subjects thus far and analyzed using 2D Page and iTRAQTM. 700 spots have been recognized using ProteomweaverTM software to analyze the gels and 207 proteins have been identified in wound samples using iTRAQTM. All wounds analyzed with iTRAQTM to date share 84 proteins, 25 proteins were only found in chronic wounds and 31 proteins were only found in healing wounds. Significant ($p<.05$) changes in the amount of proteins over the time course of the wound were found in 149 of the 207 proteins. The correlation of wound biochemistry, clinical appearance, and clinical outcome is critical to understanding of pressure ulcer healing. These findings will aid in the development of criteria for evaluating the healing process and response to treatment.

15. SUBJECT TERMS
Chronic wound, healing, 2D Page, iTRAQTM

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
U	U	U	UU	23	**19b. TELEPHONE NUMBER** *(include area code)*

Table of Contents

INTRODUCTION

The fact that there are differences in chronic versus normal healing wounds is well documented. What is unknown at this time are the specific biomarkers associated with healing wounds, the role each of these biomarkers play in wound healing, and the biomarkers that can serve as the earliest predictors of healing. It is our hypothesis that specific cytokines, proteases, and growth factors serve as the earliest indicators of healing in chronic wounds. It is the objective of this study to identify the biomarkers associated with the earliest stages of healing in chronic wounds. The findings of this study are intended to facilitate the development a diagnostic tool, which would assist in the evaluation of the healing process.

BODY

Statement of Work

Technical Objective 1: To identify the biochemical changes that occur as a chronic wound begins the healing process.

a. Analyze fluid samples to determine proteins present
b. Identify differences between subjects and subject time points
c. Confirm protein identities

Technical Objective 2: To assess the rate of healing of the wounds analyzed.

a. Measure wound
b. Calculate trajectories of healing for wounds over time

Technical Objective 3: To evaluate the location of the biomarkers assessed.

a. Compare proteins found in different locations using protein analysis

Technical Objective 4: To identify the earliest changing biomarkers occurring in wounds which progressed toward healing.

a. Correlate the changes in wound chemistry with the rate of healing
b. Analyze the earliest biochemical changes present

Technical Objectives 1,2,3, & 4:

In order to increase enrollment in the study, the 6 sites originally approved for enrollment were augmented with an additional 9 sites for a total of 15 sites. Additionally, subjects are being reimbursed for participation in the study. As of December 31, 2007, 112 subjects have been screened and 48 have been enrolled.

Technical Objective 1

The analysis of wound fluid samples to determine the proteins present is ongoing. A sample from each subject at each time point is collected and two-dimensional polyacrylamide gel electrophoresis (2D Page) is utilized to separate the proteins based on molecular weight and isolelectric point. As previously reported, the analysis of these gels is a challenge, which has been reported often in the literature (1-4). A new software package (Proteomweaver™ Software, BioRad) has been utilized since June 2007 to analyze the gels. A protocol has been developed for gel analysis with Proteomweaver™. Gels from all subjects are analyzed and compared. Spots are matched for each individual throughout the time course of the study for both peripheral and interior samples. To date 700 spots have been recognized. Changes in spot intensity are plotted versus time and may relate to healing or chronic events.

Spots from Bio-safe colloidal coomassie stained (BioRad #161-0787) gels were first sent to the Proteomics and Mass Spectrometry facility at Tufts Medical School in November 2006. Only one protein, C reactive protein was identified with confidence from subject ID BM014 01 I. Other spots did not yield identifiable proteins of sufficient confidence to report. Trouble shooting with the mass spectrometry facility led to the use the Beckman Coulter ProteomeLab™ IgY-12 Proteome Partitioning Kits, which removes the 12 most abundant proteins (albumin, IgG, transferring, fibrinogen, IgA, α2-macroglobulin, IgM, α1-antitrypsin, haptoglogin, α1-acid glycoprotein, apolipoprotein A-I and apolipoprotein A-II) from human fluids such as plasma and serum using avian polyclonal IgY molecules.

The Multiple Affinity Removal System (Agilent Technologies, Inc.) was also used for the depletion of high-abundant proteins from human proteomic samples. A spin cartridge removes albumin, IgG, antitrypsin, IGA, transferring and haptoglobin simultaneously. Both these columns were used to determine if albumin was causing the inability to identify proteins. Samples that had been treated with each column (separate samples for each) and samples not treated were sent to both the Tufts Proteomics facility and the University of Texas Medical Branch mass spectrometry facility in April 2007. These samples were stained with SYPRO Ruby Protein Gel Stain (Bio Rad # 170-3138). The results of these samples were not conclusive and had low confidence as before.

The University of Texas Health Science Center (UTHSC) Proteomics Research Core, and specifically Dr William Dubinsky, were recommended by other researchers at the TATRC PLR in January 2007. The University of Texas Medical Branch facility was initially used because the University of Texas Health Science Center Proteomics Research Core was having equipment difficulties and referred us to that laboratory. Spots from SYPRO Ruby stained gels were sent to the UTHSC Proteomics Research Core in September and October 2007. As previously, proteins were not identified with sufficient confidence to report.

Discussions regarding the problems associated with spot identification and the goals of the project led to a decision to conduct multiplexed isobaric tagging technology (iTRAQ$_{TM}$) experiments on samples collected from the wounds. The UTHSC has extensive experience and success with this technique. iTRAQ$_{TM}$ is limited in the number of samples that can be compared in an individual analysis. Four time points are selected for analysis to determine both the proteins present and their relative changes in concentration between 4 time points. Approximately 207 proteins have been identified in wound samples using this technique. All wounds analyzed to date share 84 proteins, 25 proteins were only found in chronic wounds and 31 proteins were only found in healing wounds. Significant ($p<.05$) changes in the amount of proteins over the time course of the wound were found in 149 of the 207 proteins. For example, apolipoproteins, complement component C6 and C9 and metabolic enzymes increased in concentration in healing versus non-healing pressure ulcers. Summary tables of the data from the initial 4-plex experiments of healed and non-healed wounds are in Appendix A. Analysis of the iTRAQ$_{TM}$ data is ongoing and the comparison of this data and the 2D Page data is currently a focus of the project. iTRAQ$_{TM}$ experiments are currently limited to the

simultaneous analysis of 4 samples. It identifies and gives a relative concentration of each protein present relative to one time point. 2D Page allows the comparison of limitless samples, but only three simultaneously. Difference gel electrophoresis (DiGE) allows up to three samples to be labeled using fluorescent dyes. Samples in the current project are processed individually and combined using Proteomweaver™ software to correct for differences inherent in the 2D Page technique. Results from iTRAQ$_{TM}$ experiments will both compliment and confirm 2D Page findings.

Extensive searches for facilities to identify proteins by mass spectrometry after electrophoresis identified two laboratories with a history of success, Midwest Bio Services, LLC, Overland Park, KS and Columbia University, Protein Chemistry Core Facility, New York, NY. In November 2007, two gels were run in parallel from subject ID BM01401 I and the same spots from each gel were excised and sent to Midwest Bio Services, LLC and Columbia University, Protein Chemistry Core Facility. The samples were not depleted of albumen before 2D Page. The gels were stained with Coomassie blue and spots were sent in vials without additional fluid. Midwest Bio Services, LLC identified 2 or more proteins per spot and the Columbia University, Protein Chemistry Core Facility identified 1 or more protein per spot (Table 1).

Midwest Bio Services, LLC	Spot #	Columbia University
serum albumin S69339 Ig heavy chain V region precursor S69340 Ig heavy chain VHIII-D-JH-CH3 region	1	serum albumen C-terminal fragment
hp2-alpha haptoglobin immunoglobulin heavy chain variable region	2	haptoglobin alpha chain Ig kappa chain minor
hp2-alpha haptoglobin serum albumin S100 calcium-binding protein A8 immunoglobulin lambda light chain VLJ region immunoglobulin heavy chain constant region gamma 4	3	haptoglobin alpha chain Ig kappa chain minor
hp2-alpha haptoglobin	4	haptoglobin alpha chain
hp2-alpha haptoglobin serum albumin immunoglobulin kappa light chain VLJ region	5	haptoglobin alpha chain

Table 1. Spot identification by Midwest Bio Services, LLC and the Columbia University, Protein Chemistry Core Facility

During the last year the identification of proteins in the spots cut from 2-D gels has been a major focus. Our experience has led us to the following conclusions about the real versus perceived potential of post-electrophoretic protein identification by mass spectrometry. Laboratories using the same methods of mass spectrometry analysis have different abilities to identify proteins from spots cut from 2-D gels. Samples stored in fluid for extended periods, which is a common technique for sample preparation and shipping, are inadequate for protein identification due to surface contamination and protein leaching from the gel to the fluid compartment. The sensitivity of SYPRO is 1-10 ng/spot or band and the sensitivity of Bio-Safe ™ Coomassie G-250 is 8-28 ng/spot or band. SYPRO stain was used to achieve greater spot sensitivity on the gels. Both stains are compatible with mass

spectrometry, but SYPRO is not preferred by service laboratories. The amount of protein in a gel plug submitted for analysis influences the confidence of identification as well as the ability to identify low abundance proteins that co-localized during electrophoresis. Total protein amount present in wounds decreases with healing. This may be a function of the drying during healing or may be part of the healing process. Midwest Bio Services, LLC is a fast and efficient laboratory and we will continue to send spots to this laboratory to identify the proteins present in excised spots from 2D Page gels.

Almost every spot sent for analysis has returned more than one protein. Because proteins co-localize on the gel the proportion of the spot that can be attributed to an individual protein is not easily quantifiable utilizing 2D Page. Proteins that have broken down into large fragments are present in multiple spots. The total amount of that protein would be estimated from the fragment of highest concentration. An accurate estimate is important for determining changes in concentration of the time course of the wound. iTRAQ$_{TM}$ analysis allows the proteins amounts to be separated and compared, but is limited by the number of days comparable on each sample. Future experiments will involve trials using a non-related protein to compare several samples across multiple time points beyond 4-plexes.

Technical Objective 2:

To assess the rate of healing, the wounds were photographed and their area calculated at each time point. All wounds are separated by clinical outcome: healed during the study, healing during the study, and chronic non-healing during the study. Wound area versus the time point has been graphed as wound trajectories (Appendix B).

To further characterize the wound composition, a method to measure the percentage of granulation, eschar, and slough tissue for each wound at each time point was developed. The region of the wound represented by a single tissue type is selected using tools in Adobe Photoshop CS3 and pasted into a new layer within the same image file. This process is repeated for each tissue type using the same image, thereby eliminating the ability to select the same region twice. After calibration the area represented by each tissue is recorded. Calculations are underway for all wounds. The presence of granulation tissue is a well-known and documented indicator of healing, but the biochemical

changes that accompany a change from slough or eschar to granulation tissue are not known. These findings will provide an important indicator of the wound's progress for comparison with the iTRAQ$_{TM}$ and 2D Page findings during the time course of the healing process and specific healing events.

Technical Objective 3:

To evaluate the location of the biomarkers assessed, samples are collected from both peripheral and interior locations on each wound at each time point. The total number of spots shared between peripheral and interior as well as spots exclusive to either data set are counted using Proteomweaver^{TM} software. Table 2 summarizes the analysis of the peripheral and interior samples from several subjects.

BM ID	P	I	P+I	Unique	Shared	Not Shared	I only	P only
43	592	512	1104	704	400	304	112	192
44	547	538	1085	713	372	341	166	175
15	625	570	1195	737	458	279	112	167
2	603	590	1193	770	423	347	167	180
34	586	567	1153	702	451	251	116	135
24	659	771	1430	951	479	472	292	180

BM ID	Bio Marker Identification Number
P	Peripheral spots
I	Internal spots
P+I	Total spots, I and P
Unique	Total unique spots, I and P
Shared	Total shared unique spots, I and P
Not Shared	Total unique spots, I and P, not shared
I or P Only	Number of spots found exclusively in each wound area, I and P

Table 2. Proteomweaver^{TM} analysis of peripheral and interior samples from several subjects. iTRAQ$_{TM}$ experiments comparing interior and peripheral samples from wounds are currently being conducted.

Technical Objective 4:

To identify the earliest changing biomarkers occurring in wounds which progress toward healing, changes in spot intensity are plotted versus time. Events such as a sharp decrease in the size of the wound or a change in tissue type between time points have been subjectively identified and the 2-D Page and iTRAQ$_{TM}$ findings are being correlated. The time point samples for iTRAQ$_{TM}$ experiments are chosen in order to encompass these events.

A comparison of the total number of spots between individuals and clinical outcomes for a measure of variability is determined. As noted in Technical Objective #1 All wounds shared 84 proteins, 25 proteins were only found in chronic wounds and 31 proteins were only found in healing wounds. Significant ($p<.05$) changes in the amount of proteins over the time course of the wound were found 149 of the 207 proteins.

The current research is novel with respect to current published research in the field. There are no published studies characterizing of real-time surface biochemistry of pressure ulcers. Differential protein expression between healing and non-healing pressure ulcers has identified proteins, which may serve as indicators of wound healing. The specific proteins associated with spots of interest have not yet been identified beyond PI and MW, but it is anticipated that the identity of some of these spots will be significant with regard to our understanding of the healing of chronic wounds, as well as serving as potential biomarkers of healing.

KEY RESEARCH ACCOMPLISHMENTS

- Refinement of a protocol for mass spectrometry samples
- Identification of a mass spectrometry facility able to identify the proteins present in spots with confidence
- Development of method to utilize Proteomweaver^{TM} to analyze the 2D Page gels
- Identification of 700 spots in 2D Page gels
- Development of a method to identify and measure tissue type present in wounds

- Utilization of iTRAQ$_{TM}$ experiments to evaluate proteins present at various time points in the wounds
    - 207 proteins identified using iTRAQ$_{TM}$
    - All wounds shared 84 proteins
    - 25 proteins were only found in chronic wounds
    - 31 proteins were only found in healing wounds
    - Significant ($p<.05$) changes in the amount of proteins over the time course of the wound were found in 149 of the 207 proteins

- Mass Spectrometry SOP
    1. Gels are placed in individual polypropylene containers and stained for 24-48 hours in 200 ml of Bio Rad Bio-Safe ™ Coomassie G-250 at room temperature on a rocking platform
    2. Stained gels are rinsed twice with distilled deionized water
    3. Spots are excised using wide bore pipet tips and ejected into sterile microcentrifuge tubes
    4. Tubes are sealed securely and labeled appropriately for immediate overnight shipment at room temperature

- Proteomweaver^{TM} Analysis
    1. Import gel images captured using BioRad Gel Doc XR Imaging System as per protocol
    2. Images partitioned into analysis groups by day or sample location, internal or peripheral
    3. Set image resolution to match imported file
    4. Spot detection using program determined sensitivity to maximize signal to noise ratio in images
    5. Pair matching between all gels to create a match matrix
    6. Multimatching in 3 phases to create superspots, spots appearing in multiple gels
    7. Superspot editing by hand for grossly mismatched spots only
    8. Normalization between gels
    9. Analysis of superspots using filters including superspot frequency, location, regulation factor, and statistical significance

- Tissue Type Analysis and Measurement

1. Open image file used for area measurement and wound trajectories using Adobe© Photoshop© CS3 Extended
2. Calibrate the image using the integrated 3 cm VeV MD target and the calibrate command within the Analysis menu, set measurement scale command
3. Using the quick selection tool and magic wand with variable tolerance settings (dictated by the image), select the entire region of the wound from the image
4. Copy this region and paste it into a new layer within the same image file, the wound layer.
5. Using the selection tool, magic wand, and its associated options, select the region of the wound that represents slough from the wound layer
6. Copy this region and paste it into a new layer within the same image file
7. Repeat the process for both granulation and eschar
8. On each layer, 3 tissue types and the entire wound region, calculate the area represented and record it using the Analysis menu, record measurements command
9. Copy the data to Microsoft Excel and prepare tissue trajectory graphs by plotting the area of each tissue type as a percentage of the total wound area versus day

REPORTABLE OUTCOMES

- Abstract "Biochemical Profiles of Healing and Non-Healing Pressure Ulcers", Edsberg LE, Fries KM, Brogan MS, Wyffels JT, submitted to The Symposium on Advanced Wound Care & Wound Healing Society Meeting, April 2008

- Abstract "Wound Surface Biochemistry of Healing and Non-Healing Pressure Ulcers", Edsberg LE, Fries KM, Brogan MS, Wyffels JT, submitted to the World Union of Wound Healing Societies, Third Congress, June 2008

- A new project, "Role of Bioelectrical and Biochemical Fields in Chronic Non-Healing Wounds of People with Spinal Cord Injury", has been funded by the Ontario Neurotrauma Foundation for $211,154 for the period of 1/2008- 1/2010. This project is based on the work supported by the current award. This project will allow us to compare the biochemical profiles of pressure

ulcers in people with and without spinal cord injuries. Additionally, biochemical changes after treatment with electrical stimulation will be analyzed.

CONCLUSION

The identification of a laboratory capable of identifying the proteins present in the spots cut from 2-D gels has been a major step in the completion of the project. The utilization of iTRAQ$_{TM}$ to analyze the proteins over time in combination with the 2-D Page data provides a complementary approach to allow a more complete analysis of the proteins present in the wounds over the course of time.

No studies have been identified using 2-D Page or iTRAQ$_{TM}$ to characterize the environment of healed, healing, and non-healing pressure ulcers. The addition of the tissue type data will further elucidate the biochemical profile of wounds. The correlation of wound biochemistry, clinical appearance, and clinical outcome is critical to understanding of pressure ulcer healing. These findings will aid in the development of criteria for evaluating the healing process and response to treatment. Ultimately, this work may serve as a basis for profiling other types of wounds and decreasing the costs, suffering, and deaths due to chronic wounds of all types.

REFERENCES

1. Berth M, Moser, FM, Kolbe M, Bernhardt J. The state of the art in the analysis of two-dimensional gel electrophoresis images. Appl Microbiol Biotechnol 2007;76:1223-1243.

2. Roy A, Lee KR, Hang Y, Marten M, Raman B. Analyzing two-dimensional gel images. Technical Report.

3. Salmi J, Aittokallio T, Nyman TA, Nevalainen OS. Correcting distortions in 2D gels- a survey. TUCS Technical Report, No 653, Turku Centre for Computer Science, 2004.

4. Woodward AM, Rowland JJ, Kell DB. Fast automatic registration of images using the phase of a complex wavelet transform: Application to proteome gels. Analyst 2004; 129:542-552.

APPENDICES

Appendix A. Preliminary iTRAQ$_{TM}$ data comparing chronic non-healing and healed wounds

Appendix B. Wound Trajectories – Chronic Non-Healing, Healing, and Healed.

Preliminary iTRAQ™ data comparing chronic non-healing and healed wounds

Blue indicates significant differences (P≤.05) between timepoints

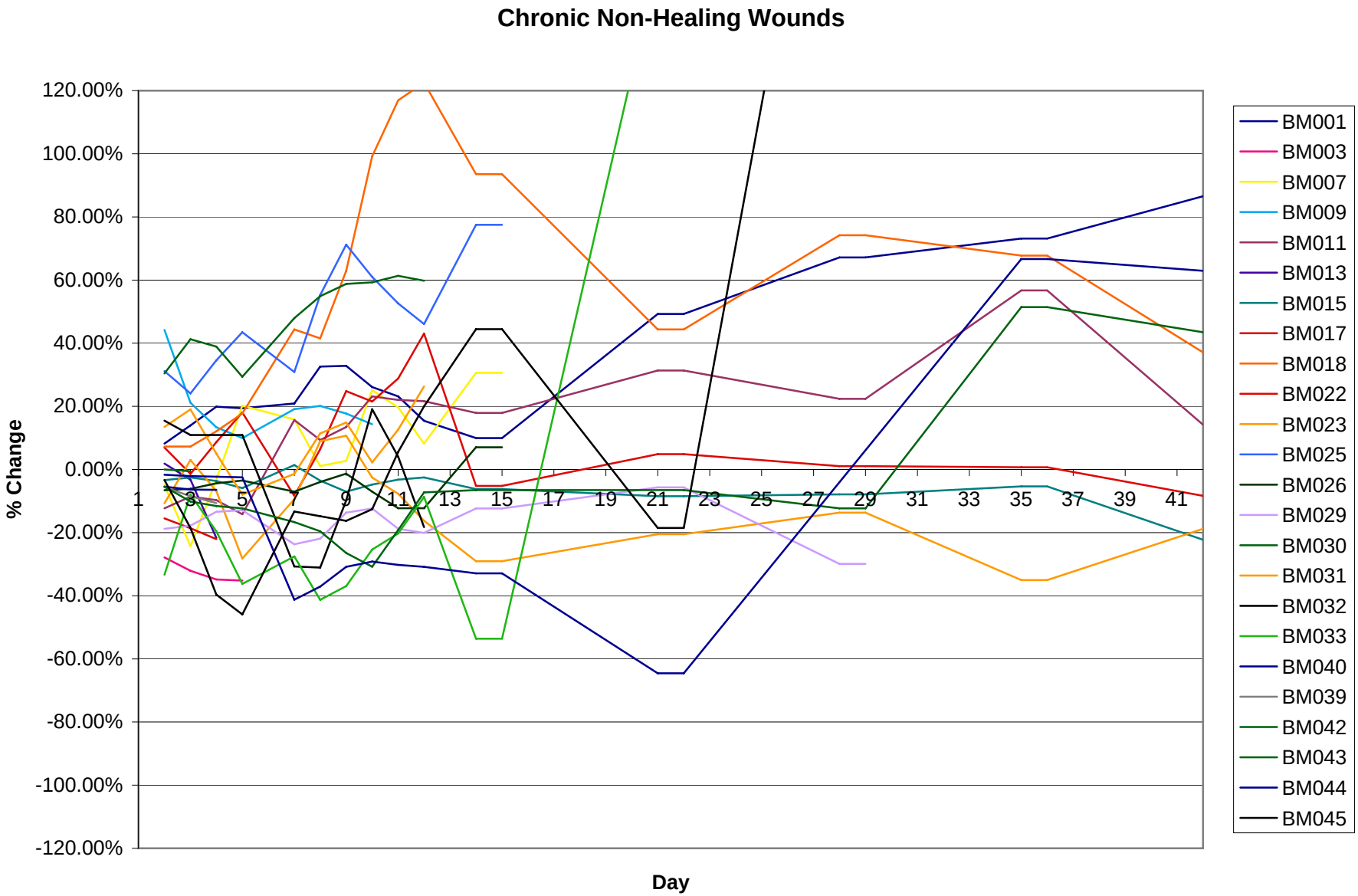
Protein Name	Ratio Day 8 / Day 2	Ratio Day 21 / Day 2	Ratio Day 42 / Day 2	Ratio Day 10 / Day 2	Ratio Day 21 / Day 2	Ratio Day 35 / Day 2	Ratio Day 14 / Day 0	Ratio Day 21 / Day 0	Ratio Day 28 / Day 0
	BM 015 Internal Chronic Non-Healing			BM 017 Internal Chronic Non-Healing			BM 027 Internal Healed		
14-3-3 protein zeta/delta (Protein kinase C inhibitor protein 1) (KCIP-1) - Homo sapiens (Human)							1.129232	1.296457	1.175607
6-phosphogluconate dehydrogenase, decarboxylating (EC 1.1.1.44) - Homo sapiens (Human)							1.506692	1.129957	1.209772
78 kDa glucose-regulated protein precursor (GRP 78) (Heat shock 70 kDa protein 5) (Immunoglobulin heavy chain-binding protein) (BiP) (E	0.970494	0.637133	0.872116	0.92187	1.02057	0.956719			
Actin, alpha cardiac muscle 1 (Alpha-cardiac actin) - Homo sapiens (Human)				1.621703	3.450181	2.00297			
Actin, cytoplasmic 1 (Beta-actin) - Homo sapiens (Human)	0.505786	1.758281	0.681029	0.984403	2.274694	1.38061	1.475409	1.720077	0.874838
Acyl-CoA-binding protein (ACBP) (Diazepam-binding inhibitor) (DBI) (Endozepine) (EP) - Homo sapiens (Human)				0.988483	0.850885	0.707514			
Adenylyl cyclase-associated protein 1 (CAP 1) - Homo sapiens (Human)	0.627318	0.983695	0.764608	2.39021	2.288312	1.466745			
Afamin precursor (Alpha-albumin) (Alpha-Alb) - Homo sapiens (Human)							0.871155	0.822324	1.114205
Alpha-1-acid glycoprotein 1 precursor (AGP 1) (Orosomucoid-1) (OMD 1) - Homo sapiens (Human)	1.202823	1.212927	1.434865	1.017341	1.185309	1.585779	0.899874	0.813504	0.935934
Alpha-1-acid glycoprotein 2 precursor (AGP 2) (Orosomucoid-2) (OMD 2) - Homo sapiens (Human)				0.845558	0.974234	1.004343			
Alpha-1-antichymotrypsin precursor (ACT) [Contains: Alpha-1-antichymotrypsin His-Pro-less] - Homo sapiens (Human)							0.384003	0.884984	0.443795
Alpha-1-antitrypsin precursor (Alpha-1 protease inhibitor) (Alpha-1-antiproteinase) - Homo sapiens (Human)	1.017016	1.350594	1.262431	0.797139	0.832148	1.01758	0.748036	0.829246	1.009776
Alpha-1B-glycoprotein precursor (Alpha-1-B glycoprotein) - Homo sapiens (Human)	1.329621	1.039383	1.110888	1.018393	0.850608	0.938225	1.02318	0.927887	1.041005
Alpha-2-HS-glycoprotein precursor (Fetuin-A) (Alpha-2-Z-globulin) (Ba-alpha-2-glycoprotein) [Contains: Alpha-2-HS-glycoprotein chain A; A				0.853367	1.184408	1.23065	0.943199	0.968551	0.978741
Alpha-2-macroglobulin precursor (Alpha-2-M) - Homo sapiens (Human)	1.339746	0.958898	1.08818	1.129772	0.954235	1.016423	0.941129	0.976435	1.04543
Alpha-actinin-1 (Alpha-actinin cytoskeletal isoform) (Non-muscle alpha-actinin-1) (F-actin cross-linking protein) - Homo sapiens (Human)	0.8061	0.860013	0.947237	1.306637	1.640309	1.612937			
Alpha-actinin-4 (Non-muscle alpha-actinin 4) (F-actin cross-linking protein) - Homo sapiens (Human)				1.311556	1.576768	1.394414			
Alpha-enolase (EC 4.2.1.11) (2-phospho-D-glycerate hydro-lyase) (Non-neural enolase) (NNE) (Enolase 1) (Phosphopyruvate hydratase) (	0.420492	1.041381	1.039288	0.929779	3.156788	1.975684	1.700044	1.379547	1.481826
AMBP protein precursor [Contains: Alpha-1-microglobulin (Protein HC) (Complex-forming glycoprotein heterogeneous in charge) (Alpha-1 n							0.963009	1	0.862874
Angiotensinogen precursor [Contains: Angiotensin-1 (Angiotensin I) (Ang I); Angiotensin-2 (Angiotensin II) (Ang II); Angiotensin-3 (Angioten	1.379253	1.054933	1.15547	0.91059	0.896993	0.96487	1.075939	0.905826	0.969975
Annexin A1 (Annexin I) (Lipocortin I) (Calpactin II) (Chromobindin-9) (p35) (Phospholipase A2 inhibitory protein) - Homo sapiens (Human)				0.56374	0.322617	0.480294			
Annexin A3 (Annexin III) (Lipocortin III) (Placental anticoagulant protein III) (PAP-III) (35-alpha calcimedin) (Inositol 1,2-cyclic phosphate 2-p	0.724071	0.961166	0.820959	0.599126	0.530294	1.161932			
Annexin A6 (Annexin VI) (Lipocortin VI) (P68) (P70) (Protein III) (Chromobindin-20) (67 kDa calelectrin) (Calphobindin-II) (CPB-II) - Homo s				1.018623	0.911313	0.932504			
Antithrombin-III precursor (ATIII) - Homo sapiens (Human)	0.906907	0.528683	0.851047				0.947207	1.023566	0.772255
Apolipoprotein A-I precursor (Apo-AI) (ApoA-I) [Contains: Apolipoprotein A-I(1-242)] - Homo sapiens (Human)							0.900082	0.854091	0.78753
Apolipoprotein A-II precursor (Apo-AII) (ApoA-II) [Contains: Apolipoprotein A-II(1-76)] - Homo sapiens (Human)							1.093398	0.907572	1.298769
Apolipoprotein B-100 precursor (Apo B-100) [Contains: Apolipoprotein B-48 (Apo B-48)] - Homo sapiens (Human)	1.51398	1.368297	1.469036				0.948203	0.896832	0.741558
Apolipoprotein C-III precursor (Apo-CIII) (ApoC-III) - Homo sapiens (Human)							0.85232	0.786706	0.418179
Apolipoprotein D precursor (Apo-D) (ApoD) - Homo sapiens (Human)							0.960774	0.876693	0.885543
Apolipoprotein E precursor (Apo-E) - Homo sapiens (Human)							0.890717	1.023588	0.529678
Arginase-1 (EC 3.5.3.1) (Type I arginase) (Liver-type arginase) - Homo sapiens (Human)	1.168742	0.855998	0.938397	0.797369	0.781151	0.766105	1.632345	1.041871	1.620156
Bactericidal permeability-increasing protein precursor (BPI) (CAP 57) - Homo sapiens (Human)	0.422038	0.879299	1.677856				1.149652	0.911462	1.057564
Beta-2-glycoprotein 1 precursor (Beta-2-glycoprotein I) (Apolipoprotein H) (Apo-H) (B2GPI) (Beta(2)GPI) (Activated protein C-binding protei	1.773897	1.300092	1.204519	0.764676	0.619496	0.58655			
Brain acid soluble protein 1 (BASP1 protein) (Neuronal axonal membrane protein NAP-22) (22 kDa neuronal tissue-enriched acidic protein)				0.810591	0.763748	0.789066			
Calmodulin (CaM) - Homo sapiens (Human)	0.913864	0.848611	1.268676	1.561937	1.328073	1.206693			
Calmodulin-like protein 3 (Calmodulin-related protein NB-1) (CaM-like protein) (CLP) - Homo sapiens (Human)	0.818409	0.601364	0.972782						
Carbonic anhydrase 1 (EC 4.2.1.1) (Carbonic anhydrase I) (Carbonate dehydratase I) (CA-I) - Homo sapiens (Human)	0.779357	0.370132	0.350427				0.784272	1.258183	0.910255
Carbonic anhydrase 2 (EC 4.2.1.1) (Carbonic anhydrase II) (Carbonate dehydratase II) (CA-II) (Carbonic anhydrase C) - Homo sapiens (Human)							0.795393	1.211879	1.01006
Carcinoembryonic antigen-related cell adhesion molecule 8 precursor (Carcinoembryonic antigen CGM6) (Nonspecific cross-reacting antige				0.969522	0.732806	0.590277			

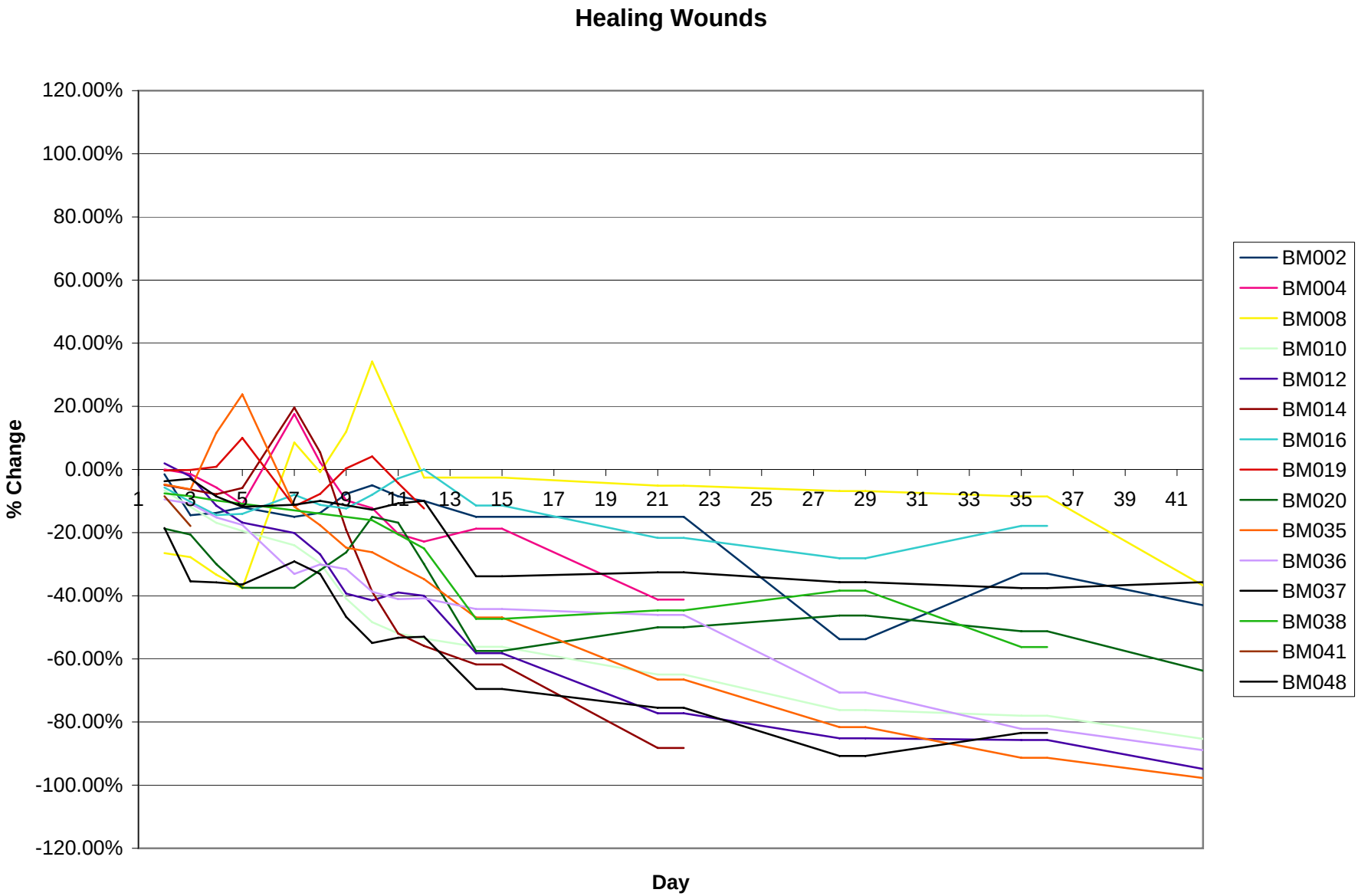
Protein Name	Ratio Day 8 / Day 2	Ratio Day 21 / Day 2	Ratio Day 42 / Day 2	Ratio Day 10 / Day 2	Ratio Day 21 / Day 2	Ratio Day 35 / Day 2	Ratio Day 14 / Day 0	Ratio Day 21 / Day 0	Ratio Day 28 / Day 0
	BM 015 Internal Chronic Non-Healing			BM 017 Internal Chronic Non-Healing			BM 027 Internal Healed		
Catalase (EC 1.11.1.6) - Homo sapiens (Human)	1.059758	0.800723	0.825065	0.855885	0.653839	0.575382	1.258211	1.151517	1.131735
Cathelicidin antimicrobial peptide precursor (18 kDa cationic antimicrobial protein) (CAP-18) (hCAP-18) [Contains: Antibacterial protein FAL	1.778766	1.269526	1.270874	1.06271	1.063733	0.830182			
Cathepsin D precursor (EC 3.4.23.5) [Contains: Cathepsin D light chain; Cathepsin D heavy chain] - Homo sapiens (Human)	0.977354	1.407499	1.241822						
CD5 antigen-like precursor (SP-alpha) (CT-2) (IgM-associated peptide) - Homo sapiens (Human)							1.069228	0.947761	0.865077
Ceruloplasmin precursor (EC 1.16.3.1) (Ferroxidase) - Homo sapiens (Human)	1.525576	1.247032	1.222681	1.105568	0.855976	0.800991	0.97229	0.959955	0.926543
Chitotriosidase-1 precursor (EC 3.2.1.14) (Chitinase-1) - Homo sapiens (Human)	0.951247	0.482707	0.859519						
Clusterin precursor (Complement-associated protein SP-40,40) (Complement cytolysis inhibitor) (CLI) (NA1/NA2) (Apolipoprotein J) (Apo-J)							1.168625	0.907515	0.924557
Cofilin-1 (Cofilin, non-muscle isoform) (18 kDa phosphoprotein) (p18) - Homo sapiens (Human)							2.139933	1.119522	0.769827
Collagen alpha-1(I) chain precursor - Homo sapiens (Human)	1.527556	1.363641	1.751762	1.45917	0.861788	0.871505	0.667168	0.637055	2.234284
Collagen alpha-1(III) chain precursor - Homo sapiens (Human)	1.0377	1.584466	1.684648						
Collagen alpha-3(VI) chain precursor - Homo sapiens (Human)	1.444809	1.466451	1.387775						
Complement C3 precursor [Contains: Complement C3 beta chain; Complement C3 alpha chain; C3a anaphylatoxin; Complement C3b alpha	1.315333	0.903001	1.02119	1.373852	1.649911	1.692482	1.039757	1.008745	0.966991
Complement C4-B precursor (Basic complement C4) [Contains: Complement C4 beta chain; Complement C4-B alpha chain; C4a anaphyla	1.048166	0.972922	1.037494	1.309388	1.878643	2.116735	1	0.952424	0.689057
Complement component C6 precursor - Homo sapiens (Human)							0.992074	1.089605	1.055459
Complement component C9 precursor [Contains: Complement component C9a; Complement component C9b] - Homo sapiens (Human)							1.437214	1.197368	1.2649
Complement factor B precursor (EC 3.4.21.47) (C3/C5 convertase) (Properdin factor B) (Glycine-rich beta glycoprotein) (GBG) (PBF2) [Cor	0.78903	0.755239	0.769224				0.969337	0.971385	0.887822
Complement factor H precursor (H factor 1) - Homo sapiens (Human)	1.089304	1.12983	1.201284	1.14119	1.354364	1.68833	0.969809	0.932514	0.740805
Complement factor I precursor (EC 3.4.21.45) (C3B/C4B inactivator) [Contains: Complement factor I heavy chain; Complement factor I light							1.145406	1.04305	1.155984
Coronin-1A (Coronin-like protein p57) (Coronin-like protein A) (Clipin-A) (Tryptophan aspartate-containing coat protein) (TACO) - Homo sap	0.961136	1.001456	0.96953	0.664773	0.931996	0.863873	1.165928	1.11607	1.014085
cra|hCP1609934.2| keratin 1 (epidermolytic hyperkeratosis)	0.669842	0.722419	0.951622	1.751633	1.824133	1.971052	1.179016	1.244589	1.221857
cra|hCP1812051| keratin 10 (epidermolytic hyperkeratosis; keratosis palmaris et plantaris)	1.015164	0.936803	1.028927	1.627096	1.81868	2.091951			
Cystatin-B (Stefin-B) (Liver thiol proteinase inhibitor) (CPI-B) - Homo sapiens (Human)	1.045523	1.017315	1.111677						
EF-hand domain-containing protein 2 (Swiprosin-1) - Homo sapiens (Human)	1.271628	1.220385	0.616336	1.38688	0.362952	0.482297			
Epididymal secretory protein E1 precursor (Niemann-Pick disease type C2 protein) (hE1) - Homo sapiens (Human)	1.112129	0.778964	1.85334						
F-actin capping protein subunit beta (CapZ beta) - Homo sapiens (Human)				0.9565	1.057192	1.088343			
Fibrinogen alpha chain precursor [Contains: Fibrinopeptide A] - Homo sapiens (Human)	0.994152	1.168038	1.40107	1.13158	2.186853	1.778715	1.257708	0.919186	2.366752
Fibrinogen beta chain precursor [Contains: Fibrinopeptide B] - Homo sapiens (Human)	1.240124	1.323435	1.671986	1.555647	1.951689	1.641659	1.646827	1.063089	2.945279
Fibrinogen gamma chain precursor - Homo sapiens (Human)	1.049432	1.229981	1.520317	1.477162	1.734763	1.499569	1.603539	1.045156	2.890829
Fibronectin precursor (FN) (Cold-insoluble globulin) (CIG) - Homo sapiens (Human)	1.101222	1.094244	1.151099	0.939524	1.309808	0.975978	0.877824	0.719924	0.630407
Filamin-A (Alpha-filamin) (Filamin-1) (Endothelial actin-binding protein) (Actin-binding protein 280) (ABP-280) (Nonmuscle filamin) - Homo s	1.282866	0.807055	0.925953	0.599174	0.63312	0.674581			
FK506-binding protein 1A (EC 5.2.1.8) (Peptidyl-prolyl cis-trans isomerase) (PPIase) (Rotamase) (12 kDa FKBP) (FKBP-12) (Immunophilin	0.798296	0.953564	0.840016						
Fructose-bisphosphate aldolase A (EC 4.1.2.13) (Muscle-type aldolase) (Lung cancer antigen NY-LU-1) - Homo sapiens (Human)	0.277347	0.810238	0.527698	0.72899	0.517788	0.548534	1.223302	1.359445	1.573731
Fructose-bisphosphate aldolase C (EC 4.1.2.13) (Brain-type aldolase) - Homo sapiens (Human)				0.687359	0.772573	0.544004			
Gelsolin precursor (Actin-depolymerizing factor) (ADF) (Brevin) (AGEL) - Homo sapiens (Human)	0.650023	0.883398	0.824953	1.141104	1.454596	1.222243	1.29186	1.178444	1.21613
gi|1351907|sp|P02769|ALBU_BOVIN Serum albumin precursor (Allergen Bos d 6) (BSA) [Bos taurus (contaminant)]							0.921405	0.867957	0.938476
Glucose-6-phosphate isomerase (EC 5.3.1.9) (GPI) (Phosphoglucose isomerase) (PGI) (Phosphohexose isomerase) (PHI) (Neuroleukin) (N	1.315153	0.874471	0.970003	1.434572	2.442275	1.955764	1.210361	0.894578	1.340168
Glutathione S-transferase P (EC 2.5.1.18) (GST class-pi) (GSTP1-1) - Homo sapiens (Human)	0.481798	0.660497	0.602769	0.890383	0.536043	0.483011	1.651468	1.159319	1.313702
Glyceraldehyde-3-phosphate dehydrogenase (EC 1.2.1.12) (GAPDH) - Homo sapiens (Human)	1.196345	1	0.984372	0.94468	0.94074	0.845351	1.197531	1.469842	1.476517
Glycogenin-1 (EC 2.4.1.186) - Homo sapiens (Human)				0.724967	0.970772	0.828199			
Granulins precursor (Proepithelin) (PEPI) [Contains: Acrogranin; Paragranulin; Granulin-1 (Granulin G); Granulin-2 (Granulin F); Granulin-3				0.894398	0.211495	0.141284			
Haptoglobin precursor [Contains: Haptoglobin alpha chain; Haptoglobin beta chain] - Homo sapiens (Human)	1.310841	0.903012	0.99416	0.859894	0.885197	1.07853	1.016425	0.919914	0.904021
Heat shock 70 kDa protein 1 (HSP70.1) (HSP70-1/HSP70-2) - Homo sapiens (Human)	0.67569	0.9723	0.719644	0.861594	1.099412	1.038702	1.324322	1.104373	1.431772
Heat shock cognate 71 kDa protein (Heat shock 70 kDa protein 8) - Homo sapiens (Human)	0.645432	1.047579	0.973785	0.797673	1.201813	1.013107	1.060776	1.073752	0.97524
Hemoglobin subunit alpha (Hemoglobin alpha chain) (Alpha-globin) - Homo sapiens (Human)	0.706412	0.426372	0.424969	2.03691	2.329488	2.685137	0.767798	1.124677	0.728657
Hemoglobin subunit beta (Hemoglobin beta chain) (Beta-globin) - Homo sapiens (Human)	0.848878	0.514984	0.542571	2.099973	2.090272	2.124439	0.662295	1.107044	0.743779

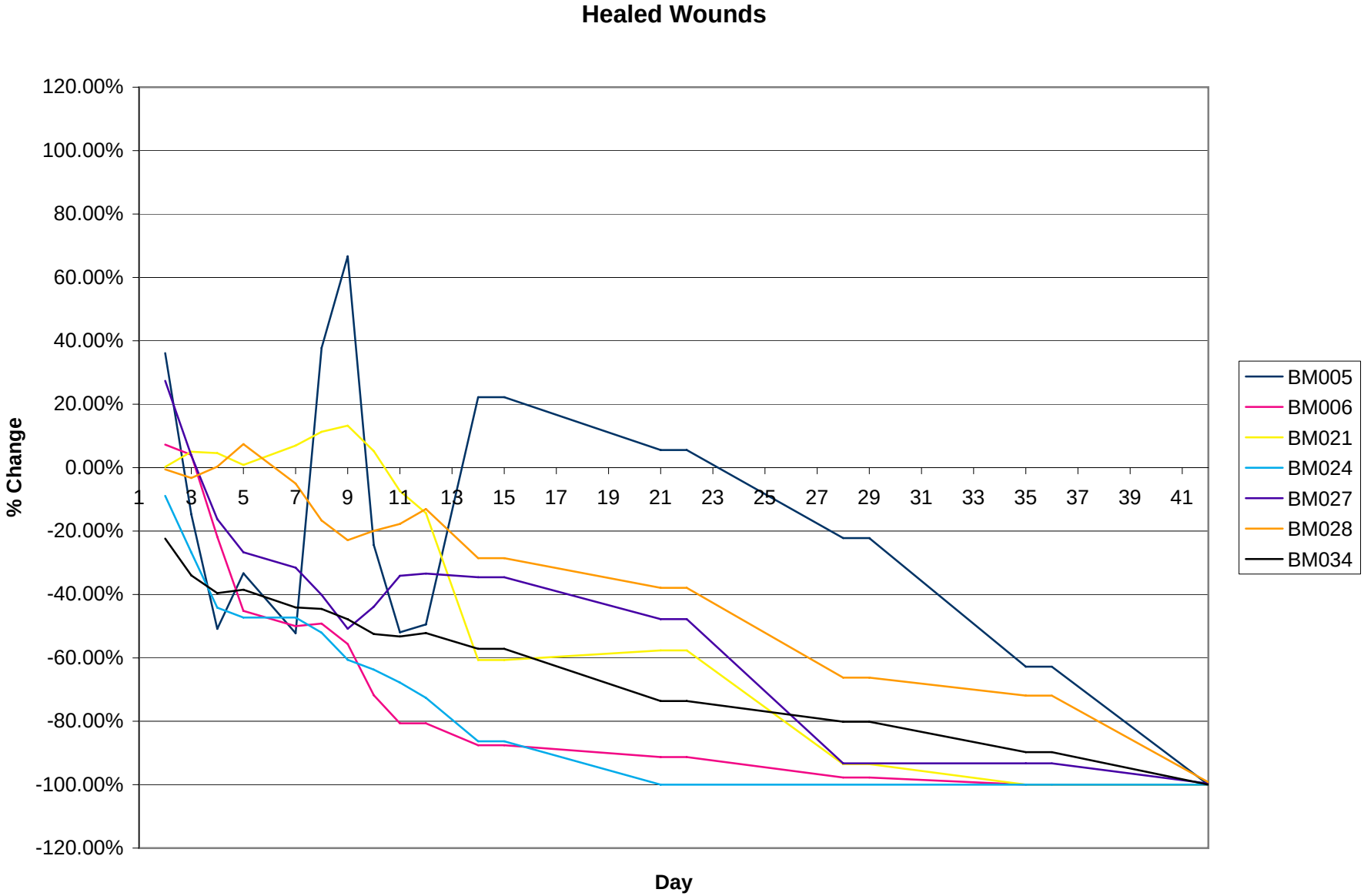
Protein Name	Ratio Day 8 / Day 2	Ratio Day 21 / Day 2	Ratio Day 42 / Day 2	Ratio Day 10 / Day 2	Ratio Day 21 / Day 2	Ratio Day 35 / Day 2	Ratio Day 14 / Day 0	Ratio Day 21 / Day 0	Ratio Day 28 / Day 0
	BM 015 Internal Chronic Non-Healing			BM 017 Internal Chronic Non-Healing			BM 027 Internal Healed		
Hemoglobin subunit delta (Hemoglobin delta chain) (Delta-globin) - Homo sapiens (Human)	0.946061	0.55981	0.795721				0.696097	1.094353	0.810552
Hemopexin precursor (Beta-1B-glycoprotein) - Homo sapiens (Human)							0.846395	1.433017	1.013671
Hemopexin precursor (Beta-1B-glycoprotein) - Homo sapiens (Human)	1.342009	1.081132	1.302712	1.126407	1.073986	1.083776	0.965689	0.904482	0.956576
Histidine-rich glycoprotein precursor (Histidine-proline-rich glycoprotein) (HPRG) - Homo sapiens (Human)	1.135209	1.009225	1.01349	1.465831	2.472499	2.504654	1.243548	0.935339	1.110639
Histone H2A type 1-D (H2A.3) - Homo sapiens (Human)	0.582307	1.554805	1.571054						
Histone H2B type 1-H (H2B.j) (H2B/j) - Homo sapiens (Human)							2.724573	1.604533	1.599977
Histone H2B type 1-L (H2B.c) (H2B/c) - Homo sapiens (Human)	0.466639	1.612041	1.297175	0.225131	0.469812	0.394226			
Histone H3.1t (H3t) (H3/t) (H3/g) - Homo sapiens (Human)	0.750311	1.548231	1.278179						
Histone H4 - Homo sapiens (Human)	0.689908	1.67732	1.398527						
Hypoxanthine-guanine phosphoribosyltransferase (EC 2.4.2.8) (HGPRT) (HGPRTase) - Homo sapiens (Human)				0.95379	0.571524	0.450103			
Ig alpha-1 chain C region - Homo sapiens (Human)	1.143247	1.086373	1.046367	0.925867	0.752291	0.899563	0.924476	0.832424	0.94101
Ig alpha-2 chain C region - Homo sapiens (Human)	1	1.350505	1.051329	1.01762	1.065072	1.15856	0.832212	0.815153	0.937972
Ig gamma-1 chain C region - Homo sapiens (Human)	1.169829	1.135863	1.073272	1.027601	0.793527	0.818362	0.932393	0.944699	0.901926
Ig gamma-2 chain C region - Homo sapiens (Human)	0.763499	1.063158	0.932792	1.289582	1.22947	1.320558	0.915019	0.86806	0.945377
Ig gamma-3 chain C region (Heavy chain disease protein) (HDC) - Homo sapiens (Human)	1.093328	1.452211	1.205379	0.944541	0.796512	0.779095	0.942456	0.834868	0.849045
Ig gamma-4 chain C region - Homo sapiens (Human)	0.915786	1.247057	1.106655	1.27511	1.496118	1.658456	0.794012	0.84475	0.884772
Ig heavy chain V-I region V35 precursor - Homo sapiens (Human)	1.116445	1.033021	0.950261	0.90089	0.922832	0.869146	0.749858	0.808205	0.886621
Ig heavy chain V-III region BRO - Homo sapiens (Human)	1.133592	1.169973	1.038824	1.017736	0.891933	1.128511	0.883677	0.944021	1.149404
Ig heavy chain V-III region CAM - Homo sapiens (Human)	1.045613	0.909751	0.778068	1.226396	1.606417	1.285284	1.014432	1.125255	1.071671
Ig heavy chain V-III region TIL - Homo sapiens (Human)	0.921534	0.789502	0.934034	1.02827	0.869138	0.988731	1.112809	1.484535	1.359113
Ig heavy chain V-III region WEA - Homo sapiens (Human)	0.783044	0.860244	0.987119	1.072752	0.532177	0.43518	0.868105	0.866295	0.912624
Ig kappa chain C region - Homo sapiens (Human)	1.191114	1.143041	1.037133	1.04526	0.96506	1	0.725236	0.941181	0.923484
Ig kappa chain V-I region AG - Homo sapiens (Human)	0.958165	1.328163	0.890397	1.218742	1.050674	1.066474	0.776307	1.157084	0.999437
Ig kappa chain V-I region DEE - Homo sapiens (Human)	1.215197	0.911596	0.911382	0.933656	1.320263	1.171657	1.046483	1.22639	1.089939
Ig kappa chain V-I region Kue - Homo sapiens (Human)	1.249914	0.983794	0.726827	1.03649	0.975124	1.037104	0.901553	0.907029	0.940031
Ig kappa chain V-II region GM607 precursor (Fragment) - Homo sapiens (Human)	0.938981	1.091882	0.891143	0.957419	0.904209	1.016983	1.190428	1.010883	1.029859
Ig kappa chain V-II region MIL - Homo sapiens (Human)	1.589738	1.875314	1.211319	1.003956	0.780389	0.781482	0.993083	1.184626	0.971859
Ig kappa chain V-II region RPMI 6410 precursor - Homo sapiens (Human)	1.05826	1.05757		0.991042	0.8383	0.965104	0.803347	0.782848	0.950525
Ig kappa chain V-III region B6 - Homo sapiens (Human)	0.914307	0.931328	0.63631	0.806429	0.772202	0.80253	0.899586	1.020587	0.983815
Ig kappa chain V-III region CLL precursor (Rheumatoid factor) - Homo sapiens (Human)	1.164283	1.087121	1.120173	1.004896	0.985974	1.241405	0.948014	0.93133	0.956675
Ig kappa chain V-III region HAH precursor - Homo sapiens (Human)	1.182093	1.106868	0.921851	1.166833	0.567072	0.628439	1.014868	0.845271	1.056289
Ig kappa chain V-III region VG precursor (Fragment) - Homo sapiens (Human)	1.033033	1.459788	0.891398	1.228726	1.098824	1.236866			
Ig kappa chain V-IV region B17 precursor - Homo sapiens (Human)	1.196412	1.021163	0.976352	0.878361	0.354296	0.471496			
Ig lambda chain C regions - Homo sapiens (Human)	1.296861	1.187278	1.018903				0.791531	0.801316	0.875201
Ig lambda chain V-I region WAH - Homo sapiens (Human)	1.457022	1.219504	0.891769				1.036671	0.905382	0.91794
Ig lambda chain V-III region LOI - Homo sapiens (Human)	1.211349	1.200563	1.007752						
Ig lambda chain V-III region SH - Homo sapiens (Human)	1.132158	1.412882	1.129454				0.863019	0.888412	0.774412
Ig lambda chain V-IV region Hil - Homo sapiens (Human)	1.402539	1.177913	0.909724				0.953217	0.827142	0.864983
Ig lambda chain V-V region DEL - Homo sapiens (Human)	1.507636	1.561906	1.065995				0.904961	0.93875	0.865026
Immunoglobulin J chain - Homo sapiens (Human)							0.977618	0.943398	0.927001
Integrin alpha-M precursor (Cell surface glycoprotein MAC-1 alpha subunit) (CR-3 alpha chain) (Leukocyte adhesion receptor MO1) (Neutro				0.878361	0.354296	0.471496			
Inter-alpha-trypsin inhibitor heavy chain H1 precursor (ITI heavy chain H1) (Inter-alpha-inhibitor heavy chain 1) (Inter-alpha-trypsin inhibitor							0.744008	1.04586	0.696357
Inter-alpha-trypsin inhibitor heavy chain H2 precursor (ITI heavy chain H2) (Inter-alpha-inhibitor heavy chain 2) (Inter-alpha-trypsin inhibitor							1.002044	0.996546	0.870269
Inter-alpha-trypsin inhibitor heavy chain H4 precursor (ITI heavy chain H4) (Inter-alpha-inhibitor heavy chain 4) (Inter-alpha-trypsin inhibitor							0.747459	0.847147	0.847961
Keratin, type I cytoskeletal 16 (Cytokeratin-16) (CK-16) (Keratin-16) (K16) - Homo sapiens (Human)	0.45649	0.342669	1.010652	1.669302	2.3745	1.425981			

Protein Name	Ratio Day 8 / Day 2	Ratio Day 21 / Day 2	Ratio Day 42 / Day 2	Ratio Day 10 / Day 2	Ratio Day 21 / Day 2	Ratio Day 35 / Day 2	Ratio Day 14 / Day 0	Ratio Day 21 / Day 0	Ratio Day 28 / Day 0
	BM 015 Internal Chronic Non-Healing			BM 017 Internal Chronic Non-Healing			BM 027 Internal Healed		
Keratin, type I cytoskeletal 9 (Cytokeratin-9) (CK-9) (Keratin-9) (K9) - Homo sapiens (Human)	0.841025	0.841904	1.10964	1.541893	1.555268	1.991621	1.033189	0.700049	0.827254
Keratin, type II cytoskeletal 6A (Cytokeratin-6A) (CK 6A) (K6a keratin) - Homo sapiens (Human)							1.167886	1.017892	1.206158
Keratin, type II cytoskeletal 6B (Cytokeratin-6B) (CK 6B) (K6b keratin) - Homo sapiens (Human)	0.725249	0.47541	0.835577	1.827205	2.242797	1.724338			
Kininogen-1 precursor (Alpha-2-thiol proteinase inhibitor) [Contains: Kininogen-1 heavy chain; Bradykinin (Kallidin I); Lysyl-bradykinin (Kallic	1.070409	0.879146	0.784537	0.921085	0.911254	1.145914	1.006036	0.994056	1.134131
Lactotransferrin precursor (EC 3.4.21.-) (Lactoferrin) (Talalactoferrin alfa) [Contains: Kaliocin-1; Lactoferroxin A; Lactoferroxin B; Lactoferro	0.818849	0.937892	1.023868	0.906367	1.123961	0.92742	1.165993	1.17189	1.12248
Lamin-B1 - Homo sapiens (Human)	1.493973	0.492161	1.081173	0.946262	0.807268	0.553704			
Leucine-rich alpha-2-glycoprotein precursor (LRG) - Homo sapiens (Human)				0.937023	0.892947	0.870765	0.972018	0.921346	0.887888
Leukocyte elastase precursor (EC 3.4.21.37) (Elastase-2) (Neutrophil elastase) (PMN elastase) (Bone marrow serine protease) (Medullasin) (Human leukocyte elastase) (HLE				1.031072	1.353349	1.112291			
Leukotriene A-4 hydrolase (EC 3.3.2.6) (LTA-4 hydrolase) (Leukotriene A(4) hydrolase) - Homo sapiens (Human)	0.771274	0.874875	0.893572	0.998811	0.915891	0.785085	1.57782	1.080141	1.481386
L-lactate dehydrogenase A chain (EC 1.1.1.27) (LDH-A) (LDH muscle subunit) (LDH-M) (Proliferation-inducing gene 19 protein) (Renal carc	0.368588	0.855923	0.696324	0.938532	0.744688	0.694044	1.289568	1.462525	1.400973
L-lactate dehydrogenase B chain (EC 1.1.1.27) (LDH-B) (LDH heart subunit) (LDH-H) (Renal carcinoma antigen NY-REN-46) - Homo sapie				1.054578	1.255389	1.386765			
Low affinity immunoglobulin gamma Fc region receptor III-B precursor (IgG Fc receptor III-1) (Fc-gamma RIII-beta) (Fc-gamma RIIIb) (FcRI				1.276185	0.392335	0.532197			
Lumican precursor (Keratan sulfate proteoglycan lumican) (KSPG lumican) - Homo sapiens (Human)							0.804707	0.938666	1.152782
Lysozyme C precursor (EC 3.2.1.17) (1,4-beta-N-acetylmuramidase C) - Homo sapiens (Human)	1.372231	0.853748	1.128481	0.643973	0.696072	0.543214	0.792167	0.858736	0.811464
Macrophage capping protein (Actin-regulatory protein CAP-G) - Homo sapiens (Human)	0.744418	0.909183	0.779378	1.2256	0.981178	0.871178	1.84118	1.365203	1.525681
Malate dehydrogenase, cytoplasmic (EC 1.1.1.37) (Cytosolic malate dehydrogenase) - Homo sapiens (Human)				1.257845	0.374129	0.398021			
Matrix metalloproteinase-9 precursor (EC 3.4.24.35) (MMP-9) (92 kDa type IV collagenase) (92 kDa gelatinase) (Gelatinase B) (GELB) [Cor	1.417179	1.147377	1.387053	0.898249	0.853272	0.911274	0.870793	0.99573	1.482412
Moesin (Membrane-organizing extension spike protein) - Homo sapiens (Human)	0.776595	0.881399	0.780273	0.484301	1	0.840518	1.383181	1.15794	1.198317
Myeloblastin precursor (EC 3.4.21.76) (Leukocyte proteinase 3) (PR-3) (PR3) (AGP7) (Wegener autoantigen) (P29) (C-ANCA antigen) (Neutrophil proteinase 4) (NP-4) - Hom				1.025172	1.160288	0.941869			
Myeloperoxidase precursor (EC 1.11.1.7) (MPO) [Contains: 89 kDa myeloperoxidase; 84 kDa myeloperoxidase; Myeloperoxidase light chai	0.648476	1.066495	1.164386						
Myosin light polypeptide 6 (Smooth muscle and nonmuscle myosin light chain alkali 6) (Myosin light chain alkali 3) (Myosin light chain 3) (M	0.721624	1.203865	0.869783						
Myosin-9 (Myosin heavy chain, nonmuscle IIa) (Nonmuscle myosin heavy chain IIa) (NMMHC II-a) (NMMHC-IIA) (Cellular myosin heavy ch	0.725521	0.917018	0.780171	0.823398	1.754161	1.841439			
Myotrophin (Protein V-1) - Homo sapiens (Human)							1.143793	1.334594	1
Neutrophil collagenase precursor (EC 3.4.24.34) (Matrix metalloproteinase-8) (MMP-8) (PMNL collagenase) (PMNL-CL) - Homo sapiens (H	0.739155	0.565476	0.664486	0.589914	0.837143	0.725397			
Neutrophil defensin 1 precursor (HNP-1) (HP-1) (HP1) (Defensin, alpha 1) [Contains: HP 1-56; Neutrophil defensin 2 (HNP-2) (HP-2) (HP2)	0.736318	0.740793	0.824349	0.470489	0.675351	0.56638			
Neutrophil gelatinase-associated lipocalin precursor (NGAL) (p25) (25 kDa alpha-2-microglobulin-related subunit of MMP-9) (Lipocalin-2) (C	1.324352	0.66185	1.003269	0.743223	0.679173	0.525782	1.07948	1.044971	1.477797
Nonsecretory ribonuclease precursor (EC 3.1.27.5) (Ribonuclease US) (Eosinophil-derived neurotoxin) (RNase UpI-2) (Ribonuclease 2) (RI	1.23309	1.456091	1.176134	1.00672	1.143142	1.192427			
Nucleoside diphosphate kinase A (EC 2.7.4.6) (NDK A) (NDP kinase A) (Tumor metastatic process-associated protein) (Metastasis inhibitio	0.594275	0.719486	0.948191	1.26493	1.758442	1.646194	1.430186	1.50436	1.558781
Peptidoglycan recognition protein precursor (PGRP-S) - Homo sapiens (Human)	0.762536	0.678908	0.985049	1.055912	1.143053	1.165282			
Peptidyl-prolyl cis-trans isomerase A (EC 5.2.1.8) (PPIase A) (Rotamase A) (Cyclophilin A) (Cyclosporin A-binding protein) - Homo sapiens	0.292821	0.650431	0.575074	1.80679	2.933963	2.40359	1.636933	1.289831	1.253808
Periostin precursor (PN) (Osteoblast-specific factor 2) (OSF-2) - Homo sapiens (Human)	1.055291	1.299169	1.44451						
Peroxiredoxin-1 (EC 1.11.1.15) (Thioredoxin peroxidase 2) (Thioredoxin-dependent peroxide reductase 2) (Proliferation-associated gene pr	0.768129	1.424791	1.302274				0.85623	1.290288	0.943654
Phosphatidylethanolamine-binding protein 1 (PEBP-1) (Prostatic-binding protein) (HCNPpp) (Neuropolypeptide h3) (Raf kinase inhibitor pro	0.857275	0.681157	0.695315						
Phosphoglycerate kinase 1 (EC 2.7.2.3) (Primer recognition protein 2) (PRP 2) - Homo sapiens (Human)							1.331385	1.185984	1.094225
Phosphoglycerate mutase 1 (EC 5.4.2.1) (EC 5.4.2.4) (EC 3.1.3.13) (Phosphoglycerate mutase isozyme B) (PGAM-B) (BPG-dependent PG	0.935559	0.658956	1.068367				1.854485	1.108134	1.518983
Pigment epithelium-derived factor precursor (PEDF) (Serpin-F1) (EPC-1) - Homo sapiens (Human)							1.055763	0.960861	0.935817
Plasma retinol-binding protein precursor (PRBP) (RBP) [Contains: Plasma retinol-binding protein(1-182); Plasma retinol-binding protein(1-1	1.255345	1.130221	1.171222	1.154376	1.03232	1.300111	0.921205	0.904007	0.996904
Plastin-2 (L-plastin) (Lymphocyte cytosolic protein 1) (LCP-1) (LC64P) - Homo sapiens (Human)	1.064675	1.060219	1.073125	1.368195	1.132209	1.121048	2.305831	1.278229	1.21782
Prickle-like protein 2 - Homo sapiens (Human)	0.953391	0.986932	0.910023						
Profilin-1 (Profilin I) - Homo sapiens (Human)	0.313338	0.64488	0.357122	0.86581	2.049277	1.611343	1.492893	1.308694	1.270226
Proteasome subunit alpha type 1 (EC 3.4.25.1) (Proteasome component C2) (Macropain subunit C2) (Multicatalytic endopeptidase comple	0.583743	0.664898	0.763106						
Protein DJ-1 (Oncogene DJ1) - Homo sapiens (Human)				0.702977	0.781773	0.830793			
Protein S100-A11 (S100 calcium-binding protein A11) (Protein S100C) (Calgizzarin) (MLN 70) - Homo sapiens (Human)				0.756322	0.695792	0.596155			
Protein S100-A6 (S100 calcium-binding protein A6) (Calcyclin) (Prolactin receptor-associated protein) (PRA) (Growth factor-inducible protei	0.788145	0.722894	1.147805	1.149602	1.055841	0.792627			
Protein S100-A7 (S100 calcium-binding protein A7) (Psoriasin) - Homo sapiens (Human)							0.871523	1.852964	1.322185

Protein Name	Ratio Day 8 / Day 2	Ratio Day 21 / Day 2	Ratio Day 42 / Day 2	Ratio Day 10 / Day 2	Ratio Day 21 / Day 2	Ratio Day 35 / Day 2	Ratio Day 14 / Day 0	Ratio Day 21 / Day 0	Ratio Day 28 / Day 0
	BM 015 Internal Chronic Non-Healing			BM 017 Internal Chronic Non-Healing			BM 027 Internal Healed		
Protein S100-A8 (S100 calcium-binding protein A8) (Calgranulin-A) (Migration inhibitory factor-related protein 8) (MRP-8) (Cystic fibrosis an	1.117501	1.519301	1.717112	1.52492	2.338407	2.374681	1.659441	0.797312	0.87595
Protein S100-A9 (S100 calcium-binding protein A9) (Calgranulin-B) (Migration inhibitory factor-related protein 14) (MRP-14) (P14) (Leukocy	1.063938	1.74336	1.863621	1.429931	2.487952	2.62221	1.662991	0.87	1.024617
Protein S100-P (S100 calcium-binding protein P) - Homo sapiens (Human)				0.823648	1.004262	0.945998			
Prothrombin precursor (EC 3.4.21.5) (Coagulation factor II) [Contains: Activation peptide fragment 1; Activation peptide fragment 2; Thromb							0.890503	0.799534	0.852926
Pyruvate kinase isozymes M1/M2 (EC 2.7.1.40) (Pyruvate kinase muscle isozyme) (Pyruvate kinase 2/3) (Cytosolic thyroid hormone-bindin	0.510268	1.32103	0.698587	1.137287	1.997339	1.540791	2.186496	1.917356	1.086688
Rab GDP dissociation inhibitor beta (Rab GDI beta) (Guanosine diphosphate dissociation inhibitor 2) (GDI-2) - Homo sapiens (Human)	0.895457	0.904793	1.01303	0.972086	0.872621	0.9002			
Ras-related C3 botulinum toxin substrate 1 precursor (p21-Rac1) (Ras-like protein TC25) - Homo sapiens (Human)	0.651342	1.003025	1.32526						
Resistin precursor (Cysteine-rich secreted protein FIZZ3) (Adipose tissue-specific secretory factor) (ADSF) (C/EBP-epsilon-regulated myelo	1.298597	0.724575	1.058878	0.655297	1.144629	0.828838			
Rho GDP-dissociation inhibitor 1 (Rho GDI 1) (Rho-GDI alpha) - Homo sapiens (Human)	0.363893	0.713333	1.196418	0.73823	1.860477	2.167448	1.217939	1.040684	1.068888
Rho GDP-dissociation inhibitor 2 (Rho GDI 2) (Rho-GDI beta) (Ly-GDI) - Homo sapiens (Human)	1.162207	0.945262	0.996731	1	2.080306	1.454576	1.460593	1.213222	1.420531
Serotransferrin precursor (Transferrin) (Siderophilin) (Beta-1-metal-binding globulin) - Homo sapiens (Human)	1.367594	1.177189	1.182196	1.041936	0.772052	0.828381	0.988571	0.937429	1.12043
Serpin B10 (Bomapin) (Protease inhibitor 10) - Homo sapiens (Human)	0.831532	0.959886	0.82875	0.520194	1.071341	1.119982	0.967175	0.842534	1.047004
Serum albumin precursor - Homo sapiens (Human)	1.543698	1.234684	1.351336	0.987727	0.567806	0.532273	0.847464	1.03422	0.7288
SH3 domain-binding glutamic acid-rich-like protein - Homo sapiens (Human)				0.747389	0.861333	0.773477			
SH3 domain-binding glutamic acid-rich-like protein 3 (SH3 domain-binding protein 1) (SH3BP-1) - Homo sapiens (Human)	0.317171	1.020206	0.825824	1.15282	1.074138	1.165941			
spt|P00760| Cationic trypsin precursor (EC 3.4.21.4) (Beta-trypsin) (Fragment)	1.019437	0.748049	0.8126	1.117345	1.332761	0.842804	0.755936	1.118293	0.892948
spt|P00761| Trypsin precursor (EC 3.4.21.4)	1.204893	0.994596	1.41753	0.940242	1.504057	0.938028	0.69981	1.248784	0.837489
Thymosin beta-4 (T beta 4) (Fx) [Contains: Hematopoietic system regulatory peptide (Seraspenide)] - Homo sapiens (Human)	0.651709	1.199257	0.854296	0.456557	1.945469	1.53616	1.943977	1.565946	1.445197
Transaldolase (EC 2.2.1.2) - Homo sapiens (Human)	0.771719	0.698909	0.666732	0.778887	0.688836	0.641404	1.703689	1.19307	1.305753
Transketolase (EC 2.2.1.1) (TK) - Homo sapiens (Human)	0.651763	0.824495	0.872333	1.318908	3.590899	2.350628	1.628318	1.435111	1.480708
Transthyretin precursor (Prealbumin) (TBPA) (TTR) (ATTR) - Homo sapiens (Human)							1.03472	0.842771	1.066977
Triosephosphate isomerase (EC 5.3.1.1) (TIM) (Triose-phosphate isomerase) - Homo sapiens (Human)	1.125817	0.883851	1.008423	1.114681	0.888964	0.758903	1.451884	1.270943	1.388557
Tropomyosin alpha-4 chain (Tropomyosin-4) (TM30p1) - Homo sapiens (Human)	0.974618	1.738728	0.69571	0.938247	0.632047	0.629771	1.185115	1.13408	1.218654
Trypsin-1 precursor (EC 3.4.21.4) (Trypsin I) (Cationic trypsinogen) (Serine protease 1) - Homo sapiens (Human)				1.066617	1.258329	1.184535			
Ubiquitin - Homo sapiens (Human)	1.527349	0.775602	0.919117	0.70223	0.909826	0.73698			
UTP--glucose-1-phosphate uridylyltransferase 1 (EC 2.7.7.9) (UDP-glucose pyrophosphorylase 1) (UDPGP 1) (UGPase 1) - Homo sapiens	0.430682	0.815032	0.951064	0.942147	1.960283	1.118908			
Vimentin - Homo sapiens (Human)	0.559176	0.60803	0.667999	0.928933	1.05371	1.041327	1.312885	1.589966	1.308008
Vinculin (Metavinculin) - Homo sapiens (Human)	0.794606	1.011144	1.136033	1.084576	1.460984	1.476244			
Vitamin D-binding protein precursor (DBP) (Group-specific component) (Gc-globulin) (VDB) - Homo sapiens (Human)	1.017341	1.050864	0.984095	1.124707	0.718127	0.806483	0.953572	0.902131	0.846702
Vitronectin precursor (Serum-spreading factor) (S-protein) (V75) [Contains: Vitronectin V65 subunit; Vitronectin V10 subunit; Somatomedin	2.562439	1.0014	1.148213				0.998296	1.670224	0.781975
WD repeat protein 1 (Actin-interacting protein 1) (AIP1) (NORI-1) - Homo sapiens (Human)	0.293175	0.557567	0.662724						
Zinc-alpha-2-glycoprotein precursor (Zn-alpha-2-glycoprotein) (Zn-alpha-2-GP) - Homo sapiens (Human)	1.266383	1.137093	1.176473	0.987071	0.733843	0.784211	0.940781	0.889174	1.020628


Chronic Non-Healing Wounds
120.00%
100.00%
80.00%
60.00%
40.00%
20.00%
0.00%
-20.00%
-40.00%
-60.00%
-80.00%
-100.00%
-120.00%
% Change
1
3
5
7
9
11
13
15
17
19
21
23
25
27
29
31
33
35
37
39
41
Day
BM001
BM003
BM007
BM009
BM011
BM013
BM015
BM017
BM018
BM022
BM023
BM025
BM026
BM029
BM030
BM031
BM032
BM033
BM040
BM039
BM042
BM043
BM044
BM045


Healing Wounds
120.00%
100.00%
80.00%
60.00%
40.00%
20.00%
0.00%
-20.00%
-40.00%
-60.00%
-80.00%
-100.00%
-120.00%
% Change
1
3
5
7
9
11
13
15
17
19
21
23
25
27
29
31
33
35
37
39
41
Day
BM002
BM004
BM008
BM010
BM012
BM014
BM016
BM019
BM020
BM035
BM036
BM037
BM038
BM041
BM048


Healed Wounds
120.00%
100.00%
80.00%
60.00%
40.00%
20.00%
0.00%
-20.00%
-40.00%
-60.00%
-80.00%
-100.00%
-120.00%
% Change
1
3
5
7
9
11
13
15
17
19
21
23
25
27
29
31
33
35
37
39
41
Day
BM005
BM006
BM021
BM024
BM027
BM028
BM034